Turning first to a formal matter, the Office Action indicated that the non-English reference submitted with the Information Disclosure Statement filed December 31, 2003 was not considered because an English translation was not provided with the reference. However, as provided in MPEP § 609 and C.F.R. § 1.98(a)(3)(I), a non-English language reference will be considered with a submission of a concise explanation of relevance. In the present situation, page 2 of the Information Disclosure Statement pointed out where in the specification a concise explanation of relevance of the non-English reference may be found. Accordingly, Applicants respectfully request consideration of the sole reference cited in the December 31, 2003 Information Disclosure Statement.

In the Office Action, Claims 1 to 9, 11 to 15, 18, 20 to 22 and 25 were rejected under 35 U.S.C. § 103(a) over WO 87/06956 (Sutherland) in view of U.S. Patent No. 6,277,628 (Johann). Claim 10 was rejected under 35 U.S.C. § 103(a) over Sutherland in view of Johann, and further in view of JP 404330300 (Miyakoshi). Claims 16, 17, 19, 23, 24 and 26 were rejected under 35 U.S.C. § 103(a) over Sutherland in view of Johann, and further in view of "Nucleic Acid Research", 1995, Vol. 23(8), pp. 1445 to 1446 (Yamamoto). The rejections are respectfully traversed since there is absolutely no motivation from the art of record for combining Sutherland's in-solution technique with Johann's dry technique, as explained below.

Sutherland describes an in-solution technique for detection of target nucleic acids, in which a sample nucleic acid is allowed to react with a probe bound to a waveguide in the presence of fluorescent dyes such as ethidium bromide. Intercalation causes fluorescent properties of the dye to change, and fluorescence is detected at the output of the waveguide, to infer the presence of the target in the sample.

Johann describes a device said to be useful for detection of hybridization results. The device comprises a capillary structure which contains a close-fitting substrate, such as capillary tube 2 which contains beads 4 (see Johann Fig. 1). Preferably, the diameter of the beads is 90% or more of the inner diameter of the capillary tube, and as a consequence of this close fit, the surface area available for hybridization is high relative to the sample volume. In use, after hybridization in which a target-probe complex has formed on the substrate, a fluorescent label such as Cy3 and/or Cy5 is added for detection of the hybridized complexes. Johann mostly contemplates detection in solution, but Example 5 at column 8 indicates that the complexes were dried before scanning for fluorescence.

In maintaining the rejection over Sutherland in view of Johann, page 3 of the Office Action took the position that "[o]ne of ordinary skill in the art at the time of the instant invention would have been motivated to apply the drying step of Johann et al. (See column 8, lines 22-32) to the method of Sutherland et al. because with the drying step, the method of Johann et al. is high throughput hybridization experiments utilizing small sample as desired (See column 2, lines 32-35). Thus, it would have been prima facie obvious to apply Johann et al. drying step to Sutherland et al.'s detection assay in order to carry out the claimed method." Applicants respectfully disagree, and submit that there is not motivation to combine the teachings of these two references.

Column 2 of Johann, which mentions the "high throughput" on which motivation is premised, provides in pertinent part as follows:

> "The present invention provides a hybridization composition which is useful in hybridization reactions where high throughput hybridization experiments utilizing small sample volumes are desired. The composition allows for hybridization experiments to be performed with sample volumes that are substantially less than

> those used today in microarray hybridization experiments. Typically, in experiments using two-dimensional microarrays, volumes for sample delivery, hybridization or washes are required in the range of 12 to 200 microliters. In contrast, when the present invention is employed, volumes in the range of 10 nanoliters to 10 microliters are necessary for sample delivery, hybridization or washes.
>
> The invention is a composition comprising one or more capillary-like casings with one or more input openings and one or more output openings and a substrate immobilized in each of said capillary-like casings. A key feature of the invention is that the substrate's surface is in close proximity with the inner surface of the capillary casing so as to minimize the ratio of liquid volume contained within said casing to the substrate's surface area. In this manner the volume for sample delivery and hybridization reactions is minimized. Typically, for two-dimensional microarrays the ratio of sample volume to surface area is about $1x10^{-5}$m. In contrast, the present invention provides for ratios of sample volume to hybridization surface area less than $1x10^{-5}$m, preferably less than $1x10^{-7}$m, and more preferably less than $1x10^{-7}$m. The ratios can be varied by changing, for example, the inner diameter of the capillary-like casing or the surface area of the substrate." Johann, col. 2, lines 33 to 62 (emphasis added).

Thus, Johann attributes his "high throughput" to the close fit between his substrate and the capillary tubes, which is said to reduce the volumes needed for hybridization while maintaining a relatively high surface area for hybridization. It is clear, therefore, that Johann himself attributes his "high throughput" to the nature of his device, and not to the drying step of Example 5. Indeed, the drying step is almost an afterthought, which follows four other examples that do not involve drying.

Moreover, Sutherland and Johann involve such completely different systems of fluorescent dyes and detection, that those of ordinary skill would not have used Johann's device in Sutherland's procedures. As explained above, Johann makes use of labeled probes, in which probes are labeled with a labeling moiety such as a fluorescent marker or dye so that the probe may be detected. In this regard, such fluorescent markers or dyes emit

fluorescence regardless of whether a hybrid forms. In this situation, the fluorescent dyes of Johann do not react with the hybrid since they are mere labels or attachments on a probe and are already emitting detectable fluorescence prior to hybridization.

In contrast, the fluorescent dyes in Sutherland are not like Johann's labels or attachments on a probe, but rather are dyes that interact with the hybrid to emit detectable fluorescence. Indeed, as explained on page 5 of Sutherland, intercalation involves the insertion of intercalatant fluorescent dyes between the strands of the double-stranded nucleic acids of a hybrid. In addition, on page 6, Sutherland indicates that one advantage of its approach is that measurement of nucleic acid hybridizations could be carried out without the necessity to pre-prepare labeled probes.

Given these differences in the nature of fluorescence and fluorescent dyes between Sutherland and Johann, one of ordinary skill in the art would not have been motivated to use Johann's device with Sutherland's procedure, and most certainly would not have been motivated to do so for the reason of "increased throughput" as otherwise conjectured in the Office Action.

In view of the foregoing, withdrawal of the § 103(a) rejections is respectfully requested.

No other matters being raised, it is believed the entire application is fully in condition for allowance, and such action is courteously requested.

Applicants' undersigned attorney may be reached in our Costa Mesa, California office at (714) 540-8700. All correspondence should continue to be directed to our below-listed address.

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